03-16-01 4-A. 03cd3

CASE 4-31268A



FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EL 138342798 US — Express Mail Label Number

3/15/01 — Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
GUITARD ET AL.
APPLICATION NO: 09/731,139
FILED: DECEMBER 6, 2000
FOR: USE OF ORGANIC COMPOUNDS

Assistant Commissioner for Patents
Washington, DC 20231

CLAIM OF PRIORITY UNDER 35 USC §119

Sir:

Applicants in the above-identified application hereby claim priority under the International Convention of Application No. 99125761.9, filed on December 23, 1999. This application is acknowledged in the Declaration of the instant case.

The certified copy of said application is submitted herewith.

Respectfully submitted,

Greg Ferraro

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134

Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6923
Date: March 15, 2001

4-31268

Europäisches Patentamt | Eur pean Patent Office | Office eur péen des brevets

# Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

**Patentanmeldung Nr. | Patent application No. | Demande de brevet n°**

99125761.9

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE, 26/10/00
LA HAYE, LE

THIS PAGE BLANK

Europäisches Patentamt | European Patent Office | Office eur péen des brevets

# Blatt 2 der Bescheinigung
# Sheet 2 of the certificate
# Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: 99125761.9

Anmeldetag:
Date of filing:
Date de dépôt: 23/12/99

Anmelder:
Applicant(s):
Demandeur(s):
Novartis AG
4058 Basel
SWITZERLAND

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Use of an insulin secretion enhancer for treating impaired glucose metabolism

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

| Staat: State: Pays: | Tag: Date: Date: | Aktenzeichen: File no. Numéro de dépôt: |
|---|---|---|

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
A61K31/198, A61P5/50

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE
Etats contractants désignés lors du dépôt:

Bemerkungen:
Remarks:
Remarques:
See for original title page 1 of the description

Dr. Dirk Hillebrand
Patentanwalt, Gruppenleiter

Novartis AG
Geistiges Eigentum Konzern
Patent- und Markenabteilung CH
CH-4002 Basel
Schweiz
Tel: +41 61 324 31 99
Fax: +41 61 322 75 32

NOVARTIS

Europäisches Patentamt
D-80298 München

**TELEFAX**
Von: +41 61 322 75 32
An: 004989 2399 4465
Total Seiten: 19

23. Dezember 1999

Ihre Ref:

Unsere Ref:
DH

**Neue Europäische Patentanmeldung (Use of Organic Compounds) - Case 4-31268P1**

Sehr geehrte Damen und Herren

Es soll heute die folgende neue Europäische Patentanmeldung mit der Bezeichung "Use of Organic Compounds" und mit der internen Kennzeichnung "Case 4-31268P1" per Fax im Namen der Novartis AG eingereicht werden.

Hierzu werden per Fax der Erteilungsantrag, die Empfangsbestätigung, der Abbuchungsauftrag sowie der Anmeldungstext beigefügt. Zusätzlich werden die entsprechende Dokumente sowie die erforderliche Anzahl Kopien der Anmeldungstexte separat mit Bestätigungsschreiben zugesandt.

Im voraus herzlichen Dank.

Im Namen der Novartis AG

Dr. Dirk Hillebrand
Zugelassener Vertreter, AV Nr. 36671

Beilage: (Per Fax einfach/Per Bestätigungsschreiben mit erforderlicher Anzahl an Kopien)
Erteilungsantrag
Empfangsbestätigung
Abbuchungsauftrag
Europäische Patentanmeldung "Use of Organic Compounds" (Case 4-31268P1)

Use of Organic Compounds

Impaired Glucose Metabolism (IGM) is an intermediate stage between normoglycemia and type 2 diabetes mellitus that includes the categories (i) Impaired Glucose Tolerance (IGT) and (ii) Impaired Fasting Glucose (IFG). Both categories may also be overlapping.

IFG is a new class within the field of diabetes conditions recently created by the American Diabetes Association (ADA) [*Diabetes Care 1998 Jan.; 21 (suppl. 1): S5-19*] defined by fasting glycemia between normal and diabetic levels. Patients with IFG may also have abnormal prandial (post-meal) glycemia (IGT); however, the proportion of patients with both abnormalities varies significantly between different countries.

IGT is characterized by prandial hyperglycemia. Many patients with IGT have some elevations of Fasting Plasma Glucose (FPG). IGT is a major risk factor for developing diabetes and is an independent risk for cardiovascular morbidity and mortality.

According to the new classification of diabetes and intermediate stages as established by the ADA in 1997, Normal Glucose Tolerance (NGT), IGM and type 2 diabetes mellitus are defined by following physiological parameters:

| | NGT | IGM | Type 2 Diabetes mellitus |
|---|---|---|---|
| | | IFG | |
| FPG level | <6.1 mmol/L (<110 mg/dl) | 6.1 - 7 mmol/L (110 - 126 mg/dl) | > 7 mmol/L > 126 mg/dl) |
| | and | and/or IGT | or |
| 2 h prandial glucose level (75 g OGTT [1]) | < 7.8mmol/l (<140 mg/dl) | 7.8 - 11.1 mmol/L (140 - 220 mg/dl) | > 11.1 mmol/L (> 200 mg/dl) |

[1] The oral glucose tolerance test (OGTT) should be performed as described by WHO using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water.

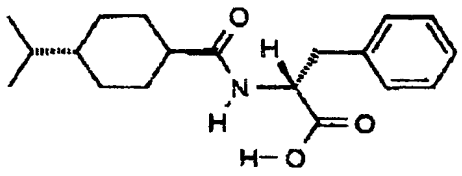
IGM is associated with following potential complications: 1.) progression to overt diabetes, 2.) increased vascular, especially cardiovascular, mortality and morbidity, and 3.) increased mortality related to cancer. Increased hyperglycemia is also associated with other metabolic disturbances such as dislipidemia, hyperuricemia as well as hypertension and angina pectoris. Accordingly, the reduction of prandial hyperglycemia will help to prevent to progress to overt diabetes and/or reduce the excessive cardiovascular morbidity and mortality observed in these subjects.

The stage between normoglycemia and type 2 diabetes mellitus is becoming of major interest and there is a strong need for a method to inhibit or delay the progression to type 2 diabetes mellitus.

It has unexpectedly been found that insulin secretion enhancers may be used to prevent to progress to overt diabetes, to reduce vascular, especially cardiovascular, mortality and morbidity and to reduce increased mortality related to cancer.

Insulin secretion enhancers are active ingredients which have the property to promote the secretion of insulin from pancreatic β-cells. Examples of insulin secretion enhancers are sulfonylureas (SU), especially those which promote the secretion of insulin from pancreatic β-cells by transmitting signals of insulin secretion via SU receptors in the cell membrane, including (but are not limited to) tolbutamide; chlorpropamide; tolazamide: acetohexamide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzensulfonamide (glycopyramide); glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; and tolylcyclamide, or a pharmaceutically acceptable salt thereof.

Insulin secretion enhancers furthermore include the new phenylalanine derivative nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] (cf. EP 196222 and EP 526171) of the formula



(I);

repaglinide [(S)-2-ethoxy-4-{2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl}benzoic acid]; representatives of the new generation of SUs such as calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinlycarbonyl)-propionate dihydrate (KAD-1229) and glimepiride (Hoe 490); and in free or pharmaceutically acceptable salt form.

Insulin secretion enhancers likewise include DPP-IV inhibitors, GLP1 and GLP1 agonists.

A preferred insulin secretion enhancer is repaglinide, most preferred is nateglinide.

The term nateglinide likewise comprises crystal modifications such as disclosed in EP 0526171 B1 or US 5,488,510, respectively, the subject matter of which, especially with respect to the identification, manufacture and characterization of crystal modifications, is herewith incorporated by reference to this application, especially the subject matter of claims 8 to 10 as well as the corresponding references to the B-type crystal modification.

These favorable effects can be verified e.g. in a multi-center, double-blind, parallel group, randomized study with patients to evaluate the incidence of confirmed hypoglycemia and the prandial effects on glucose in patients with IGM receiving nateglinide 30 mg, 60 mg or 120 mg or placebo before each main meal during 8 weeks of treatment. Patients will be selected on the basis of a 2-hour plasma glucose value after a 75 g oral glucose tolerance test (OGTT) and patients essentially meeting the following additional inclusion criteria are included in the study:

- two-hour glycemia post-OGTT between 7.8 to 11.1 mmol/L (one OGTT performed during the year before entering the study, the second to be performed within two weeks prior entering the study);
- FPG < 7 mmol/L;
- patients having a body mass index (BMI) between 20-32 kg/m2;
- patients who maintain prior diet during the full course of study;

- males, non-f rtile females, females of child-bearing potential using a medically approved birth control method;
- the use of further antidiabetics during the trial is not permitted.

Corresponding dosages of e.g. nateglinide are administered with a large glass of water 2 (BID), 3 (TID) or 4 (QID) times daily depending on the number of main meals (breakfast, lunch, snack, dinner). The first dose is given with the first main meal (standardized meal i.e. 55% carbohydrates, 25% fat and 20% protein). Visits are scheduled to be performed at weeks 0, 2, 4 and 8 and the patient have fasted for at least 7 hours. All blood samples for laboratory evaluations are drawn between 07.00 and 10.00 a.m.. HbA1c is measured at baseline and after 8 weeks of treatment (fasting glucose and fructosamine). Samples of blood are drawn at 10, 20, 20, 60, 120, and 180 minutes after drug administration (time 0) and the glucose and insulin levels are measured. At weeks 0 and 8 visits, patients complete a standard meal challenge containing approximately 500 kcal with measurements of insulin and glucose.

The analysis of all obtained data clearly reveal that FPG and 2h prandial glucose concentrations are surprisingly and significantly reduced and that e.g. nateglinde prevents the progression of conditions and diseases associated with IGM to type 2 diabetes mellitus.

Accordingly, the present invention relates to a method of prevention of progression to overt diabetes, especially of type 2, to a method of reduction of increased vascular, especially cardiovascular, morbidity and mortality. and to a method of reduction of mortality related to cancer, comprising administering to a subject in need thereof an effective amount of an insulin secretion enhancer or a pharmaceutically acceptable salt thereof. A subject in need of such method is a warm-blooded animal including man.

The present invention also relates to a method of prevention of cardiovascular complications associated with IGM and of prevention of progression to type 2 diabetes mellitus in subjects with IGM and associated diseases and conditions such as isolated prandial hyperglycemia.

The present invention likewise relates to a method of treatment of conditions and disease associated with IGM.

The present invention likewise relates to a method of treatment or prevention of conditions and diseases associated with IGT or isolated postmeal (prandial) hyperglycemia, respectively.

Diseases and conditions associated with IGT, isolated postmeal hyperglycemia and/or IFG include obesity, increased age, family history of diabetes, diabetes during pregnancy, dislipidemia, high blood pressure, uricemia, insulin resistance, angina pectoris, myocardial infarction, and stroke.

Preferably, said preventions should be effected in patients with prandial glucose excursions in the diabetic range (2 hours plasma glucose from 7.8 to 11.1 mmol/L after an OGTT).

The present invention relates to the use of an insulin secretion enhancer or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the prevention of progression to overt diabetes, especially of type 2, for the reduction of increased vascular, especially cardiovascular, morbidity and mortality, and for the reduction of mortality related to cancer.

The present invention relates to the use of an insulin secretion enhancer or a pharmaceutically acceptable salt for the manufacture of a medicament for the prevention of cardiovascular complications associated with IGM and of prevention of progression to type 2 diabetes mellitus in subjects with IGM and associated diseases and conditions such as isolated prandial hyperglycemia.

The present invention relates to a pharmaceutical composition for prevention of progression to overt diabetes, especially of type 2, to a method of reduction of increased vascular, especially cardiovascular, morbidity and mortality, and to a method of reduction of mortality related to cancer comprising an insulin secretion enhancers or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention relates to a pharmaceutical composition for the pr vention of progression to type 2 diabetes mellitus, for the prevention of cardiovascular complications

associated with IGM and of prevention of progression to type 2 diabetes mellitus in subjects with IGM and associated diseases and conditions such as isolated prandial hyperglycemia.

The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

Pharmaceutically acceptable salts e.g. of nateglinide are, for example, salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, as well as ammonium salts.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carries, especially suitable for enteral or parenteral application.

The novel pharmaceutical preparations contain, for example, from about 10 % to about 100 %, preferably 80%, preferably from about 20 % to about 60 %, of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

Nateglinide (I) is preferably administered to the warm-blooded animal in a dosage in the range of about 5 to 1200, more preferably 25 to 800, mg/day, when the warm-blooded animal is a human of about 70 kg body weight. Preferred dosages contain 30mg, 60mg or 120mg of nateglinde to be administered preferably before the main meals. Depending on the number of main meals the dose regimen are two times a day (BID) or three times a day (TID) or four times a day (QID).

The following Examples illustrates the invention described above; they are not, however, intended to limit the scope of the invention in any way.

Example 1: Tablets of Nateglinide (I)

216,000 tablets, each which contain 120 mg of nateglinide (I) are prepared as follows:

| | | |
|---|---|---|
| Composition: | nateglinide (I) | 12.960 kg |
| | lactose, NF | 30.564 kg |
| | microcrystalline cellulose, NF | 15.336 kg |
| | povidone, USP | 2.592 kg |
| | croscarmellose sodium, NF | 3.974 kg |
| | colloidal silicon dioxide, NF | 1.382 kg |
| | magnesium stearate, NF | 1.231 kg |
| | coating: opadry yellow | 1.944 kg |
| | purified water, USP* | Q.S. |

*: removed during process

Preparation process: The microcrystalline cellulose, povidone, part of the croscarmellose sodium, nateglinide (I) and lactose are mixed in a high shear mixer and afterwards granulated using purified water. The wet granules are dried in a fluid bed dryer and passed through a screen. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the dried granules in a V-blender. The magnesium stearate is passed through a screen, blended with the blend from the V-blender and afterwards the total mixture is compressed to tablets. The opadry yellow is suspended in purified water and the tablets are coated with the coating suspension.

Example 2: Galenic Formulation of Nateglinide (I) No. 1

| | |
|---|---|
| intra-granular: | |
| nateglinide (I) | 120 mg |
| lactose monohydrate | 283 mg |
| microcrystalline cellulose | 142 mg |
| povidone | 24 mg |
| croscarmellose sodium | 24 mg |
| extra-granular: | |
| magnesium stearate | 7 mg |
| opadry white | 20 mg |

Example 3: Galenic Formulation of Nateglinide (I) No. 2

| | |
|---|---|
| intra-granular: | |
| nateglinide (I) | 120 mg |
| lactose monohydrate | 283 mg |
| microcrystalline cellulose | 142 mg |
| povidone | 24 mg |
| croscarmellose sodium | 24 mg |
| extra-granular: | |
| croscarmellose sodium | 12.8 mg |
| magnesium stearate | 11.4 mg |
| opadry yellow | 18.0 mg |
| colloidal silicon dioxide | 12.8 mg |

What is claimed is

1. The use of an insulin secretion enhancer or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the prevention of progression to overt diabetes, especially of type 2, for the reduction of increased vascular, especially cardiovascular, morbidity and mortality, and for the reduction of mortality related to cancer.

2. Use according to claim 1 for the manufacture of a medicament for the prevention of cardiovascular complications associated with IGM and of prevention of progression to type 2 diabetes mellitus in subjects with IGM and associated diseases and conditions such as isolated prandial hyperglycemia.

3. Use according to claim 1 or 2 for the prevention of cardiovascular complications associated with IGM and of prevention of progression to type 2 diabetes mellitus in subjects with IGM and associated diseases and conditions such as isolated prandial hyperglycemia.

4. Use according to any one of claims 1 to 3 for the treatment or prevention of conditions and diseases associated with IGT or isolated prandial hyperglycemia, respectively.

5. Use according to claim 4 for the treatment of diseases and conditions associated with isolated postmeal hyperglycemia and/or IFG including obesity, increased age, family history of diabetes, diabetes during pregnancy, dislipidemia, high blood pressure, uricemia, insulin resistance, angina pectoris, myocardial infarction, and stroke.

6. Use according to any claim 4 for the prevention in patients with prandial glucose excursions in the diabetic range (2 hours plasma glucose between 7.8 to 11.1 mmol/L after an OGTT).

7. Use according to claim 1 for the treatment or prevention of conditions and diseases associated with IFG.

8. Use according to any one of claims 1 to 7 wherein an insulin secretion enhancer is selected from a sulfonylurea, repaglinide, nateglinide, a DPP-IV inhibitor, GLP1 and a GLP1 agonist, or, in each case, a pharmaceutically acceptable salt thereof.

9. Use according to claim 8 wherein the insulin secretion enhancer is nateglinide or a pharmaceutically acceptable salt thereof.

Abstract

Use of Organic Compounds

The invention relates to the use of an insulin secretion enhancer or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the prevention of progression to overt diabetes, especially of type 2, for the reduction of increased vascular, specially cardiovascular, morbidity and mortality, and for the reduction of mortality related to cancer.